REMARKS

Introductory Comments

Reconsideration of the above-identified application in view of the above amendments and arguments set forth is respectfully requested.

Claims 18, 20-29 and 36-38 are pending and under consideration. Claims 30-35 have been canceled in response to the restriction requirement. Additionally, claim 19 has been canceled in this Amendment. Applicants reserve the right to pursue these claims in one or more divisional applications.

Claims 18, 20-29 have been amended and claims 36-38 have been added as explained below. No new matter has been added as a result of these amendments.

Objection of Claims 22-29 Under 37 C.F.R. 1.75(c)

Claims 22-29 are objected to under 37 C.F.R. 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other dependent claim.

Additionally, claim 22 is objected to because in line 2, "nucleic" is misspelled. Claim 26 is objected to because in line 5, "promoter" is misspelled. Claim 29 is objected to because in line 2, "promoter" is misspelled.

Claims 20, 22, 24, 25 and 27-29 have been amended to change the claim dependency and Applicants submit claims 22-29 now do not contain any improper multiple dependencies. Additionally, claims 36-38 have been added which correspond to claims 22-24, respectively. These claims depend on claim 18 instead of claim 21.

With respect to claim 22, Applicants respectfully submit that "nucleic" (twice occurrence) is properly spelled.

With respect to claims 26 and 29, Applicants have corrected the misspelling of "promotor". Applicants thank the Examiner for pointing out the deficiencies of the claims.

Additionally, Applicants have amended claim 26, by making minor changes to the claim language. Specifically, claim 26 is now clearer by reciting "wherein the only cells that survive are those that express the vector" instead of "wherein only cells will survive expressing the vector".

Finally, Applicants have amended claim 23 by deleting "a" and inserting "an" therefor in order to place the claim in a better format.

Accordingly, Applicants respectfully request withdrawal of the objection of claims 22-29 under 37 C.F.R. 1.75(c).

Rejection of Claims 19-23 and 25-28 Under 35 U.S.C. § 102(b)

Claims 19-23 and 25-28 are rejected under 35 U.S.C. § 102(b), as being anticipated by Barber *et al.*, WO 98/32880 (herein "Barber").

Specifically, the Examiner asserts that Barber discloses a method for identification of an intramer capable of binding to and modifying the function of a functional intracellular target as claimed (Barber at page 4, paragraph 2, page 5, paragraphs 1-2, page 32, paragraph 3, page 49, paragraph 2 and page 16, paragraphs 2-3).

Applicants respectfully traverse this rejection.

The present invention relates to the intracellular application of functional nucleic acids, termed "intramers" (specification, page 1, first paragraph). The intramers are able to bind, modulate or catalytically modify an intracellular target thereby affecting its biological function (pages 3-4). The present invention is based on the unique insight that nucleic acid ligands can be targeted against practically any cellular component, and can be easily applied intracellularly whereby

a) they still recognize their target in the intracellular environment;

b) they can do so even with targets that are non-nucleic acid-binding by nature;

c) they can localize their target in subcellular compartments such as the cytoplasmic face of the cell membrane where nucleic acids are normally not found;

d) they can modulate the biological function of the target which allows conclusions with respect to its biological role; and

e) they can alter the phenotype of the cell (page 5).

Barber discloses a hairpin ribozyme library in order to identify gene products that produce phenotypic effects (abstract). Barber specifically targets and inactivates RNAs (page 1, first paragraph, page 3, first paragraph and page 4, first paragraph). While Barber discloses examining phenotypic effects using the hairpin ribozyme library, Barber does not disclose nor teach preparing a candidate intramer mixture of nucleic acids, contacting the candidate intramer mixture of nucleic acids with the intracellular target or part thereof whereby the target or the part thereof is not known to bind to RNA, allowing an intramer to find its target inside an intracellular compartment which includes, but is not limited to, targets specifically on a cytoplasmic face and change the cell's phenotype.

Additionally, Barber, page 16, first paragraph, discloses that the target sequences are total cellular DNA or RNA. It appears that the targets of Barber are polynucleotides that are in the nucleus region of the cell or in an environment where there are no concerns of competition from other intracellular molecules during the complexing between the target and the ribozymes. Thus, Barber does not disclose nor suggest Applicant's method wherein the candidate intramer finds its target in a specific intracellular compartment, nor does Barber appreciate the concerns of competitive binding of the many other molecules with an intramer. While on page 27, Barber discloses the transfer of nucleic acids into cells, it appears that the disclosure pertains to transfection of cells with known gene sequence found after prior studies of phentotypic effects via the disclosed ribozymes. Applicants' claim 18 specifically requires contacting the candidate intramer mixture of nucleic acids with the intracellular target or part thereof whereby the target or the part thereof is not known to bind RNA prior to step (b).

In an effort to further prosecution of the instant application, Applicants have amended claims 18 and 21 to recite "by a mechanism different from an antisense mechanism". Support for this amendment can be found on page 16, lines 18-23, *inter alia*.

Applicants will now discuss the claims with respect to this amendment.

First, the preamble states that the claimed method relates to identification of an intramer. Intramers are different from the ribozymes which are disclosed in Barber (see Barber, page 4, lines 2-3), as explained further below. Barber's method uses an anti-sense mechanism by base pairing at the mRNA level as this is the site of action of ribozymes. However, Applicants' claims 18 and 21 now recite "by a mechanism different from an anti-sense mechanism" which defines the intramer used or present in step a) of the claimed methods, where a candidate intramer mixture of nucleic acids is prepared. Therefore, the claimed methods and Barber's method are different in terms of ingredients or starting materials used.

As stated above, Barber's method uses ribozymes instead of intramers, which have a completely different mode of action when compared to each other. The term "intramer" as used in the present invention describes aptamers which are used in an intracellular environment (page 1, line 4). Aptamers are functional nucleic acids which assume a distinct 3D-structure which allows them to specifically interact with other molecules. Such interaction is not based on an anti-sense mechanism (i.e., Watson-Crick base pairing or the like), but more resembles the key-lock model known from antigens and antibodies or substrates and enzymes. Aptamers can be generated, e.g., by providing a library of about 10^{14} to 10^{18} different nucleic acids and out of these nucleic acids those specifically binding to a target molecule can be selected. See specification, pages 3 and 4.

Applicants have surprisingly found that aptamers can be used to bind and modulate the function of an intracellular target. Pages 27 and 28 of the specification disclose that prior studies suggest to the contrary, that aptamers would not be active in an intracellular environment. The reason for this is because an *in vitro* selected aptamer specifically finds the target it has been selected for but would also interact with other proteins, including RNA-binding proteins which usually have a high affinity also for sequence independently bound ribonucleic acids.

However, Applicants have surprisingly found that given the rather high affinities of the professional RNA-binding proteins for aptamers, the aptamers were still able to identify their target inside a cell and change the cell's phenotype. Additionally, despite a comparatively low affinity to their cognate intracellular targets, aptamers still recognize them with an unexpected specificity. Finally, Applicants have found that aptamers even act in cellular sub-compartments in which nucleic acids normally do not appear.

Applicants herewith attach a paper by Eaton *et al.*, "Let's get specific: the relationship between specificity and affinity", Chemistry and Biology, Vol. 2, pp. 633-638, 1995 (herein "Eaton"). On page 637, right column, last paragraph, Eaton describes a theoretical aptamer binding to its target with a KD of 10^{-10} and being confronted with 100 proteins binding inspecifically with a KD of 10^{-9}. Under such conditions, only 1.86% of the aptamers can bind to the proper target while the remaining aptamers are bound by different proteins. Conversely, Applicants have demonstrated and disclosed in the present application that their aptamer is bound by RNA binding proteins better by a factor of 1000 compared to the binding through its proper target, but surprisingly is still capable of binding to its proper target such as to affect the phenotype of the cell.

Accordingly, Applicants respectfully request withdrawal of the rejection of claims 19-23 and 25-28 are rejected under 35 U.S.C. § 102(b), as being anticipated by Barber *et al.*, WO 98/32880.

Rejection of Claim 24 Under 35 U.S.C. § 103(a)

Claim 24 is rejected under 35 U.S.C. § 103(a), as being unpatentable over Barber *et al.*, WO 98/32880 (herein "Barber") in view of Kolanus *et al.*, Cell, July 26, 1996 (herein "Kolanus").

Specifically, the Examiner asserts that Barber does not disclose that the functional intracellular target is an integrin. However, the Examiner asserts that Kolanus teaches using integrin as a functional intracellular target in order to evaluate the effects of inactivating integrin in a cellular system (page 234, column 1, first paragraph).

Applicants respectfully traverse this rejection.

Claim 24 is dependent upon claim 21. Kolanus does not remedy the deficiencies of Barber as stated above with respect to claim 21. Applicants' arguments are incorporated herein. Specifically, although Kolanus discloses that it is beneficial to study the effects of inactivating integrin in a cellular system, Kolanus does not appreciate the complexity or problems of studying integrin using intramers which Applicants use and solve.

Accordingly, Applicants respectfully request withdrawal of the rejection of claim 24 under 35 U.S.C. § 103(a), as being unpatentable over Barber *et al.*, WO 98/32880 in view of Kolanus *et al.*, Cell, July 26, 1996.

Rejection of Claim 29 Under 35 U.S.C. § 103(a)

Claim 29 is rejected under 35 U.S.C. § 103(a), as being unpatentable over Barber *et al.*, WO 98/32880 (herein "Barber") in view of Clackson *et al.*, U.S. Patent No. 6,649,595 (herein "Clackson").

Specifically, the Examiner asserts that Barber does not disclose using an IL-2 promoter to drive gene expression. However, the Examiner asserts that Clackson teaches using an IL-2 promoter to drive gene expression (column 115, lines 51-60).

Applicants respectfully traverse this rejection.

Claim 29 is dependent upon claim 26. Clackson discloses methods and materials for multimerizing chimeric proteins in genetically engineered cells using improved rapalogs while avoiding the immunosuppressive effects of rapamycin (column 2, lines 39-42). While Clackson teaches using an IL-2 promoter to drive gene expression (column 115, lines 51-60), Applicants respectfully submit that Clackson does not remedy the deficiencies of Barber as noted above. Applicants' arguments with respect to the deficiencies of Barber are incorporated herein.

Accordingly, Applicants respectfully request withdrawal of the rejection of claim 29 under 35 U.S.C. § 103(a), as being unpatentable over Barber *et al.*, WO 98/32880 in view of Clackson *et al.*, U.S. Patent No. 6,649,595.

CONCLUSION

Applicants respectfully submit that the claims comply with the requirements of 35 U.S.C. Sections 102 and 103. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Should the Examiner have any questions concerning the above, she is respectfully requested to contact the undersigned at the telephone number listed below. If the Examiner notes any further matters which the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned.

If any additional fees are incurred as a result of the filing of this paper, authorization is given to charge deposit account no. 23-0785.

Respectfully submitted,
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